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Am J Clin Pathol 1994 Jul;102(1):76-9

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Cancer Res 1994 Jun 15;54(12):3260-6

Cancer 1992 Nov 15;70(10):2493-8

J Histochem Cytochem 1991 Sep;39(9):1281-7

J Clin Pathol 1992 Aug;45(8):726-7

J Clin Immunol 1991 May;11(3):117-27

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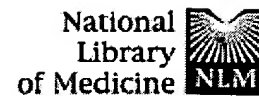
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p53 protein and c-erbB-2 protein (p185) expression in endometrial adenocarcinoma of endometrioid type. An immunohistochemical examination on paraffin sections.

Nielsen AL, Nyholm HC.

Department of Pathology, Bispebjerg Hospital, Copenhagen, Denmark.

The expression of both the nuclear protein p53 tumor suppressor gene product and the transmembrane C-erbB-2 protein oncogene product (p185) correlates to risk factors and outcomes in different tumor types. Their value as prognosticators in endometrial adenocarcinoma of endometrioid type (EC) has not been determined. Paraffin sections were examined immunohistochemically to study the expression of p53 protein and p185 in 112 patients with EC. p53 protein was overaccumulated in 34% and p185 in 13% of the tumors. p53 protein correlated with mitotic count and nuclear grade. Both p53 protein and p185 correlated significantly with outcome. However, they did not correlate with each other or with architectural grade or stage (which defines a high risk group), indicating a role as adjuvant prognosticators in EC. Stage and outcome did correlate, however. Both p53 protein and p185 antibodies work well on routine, formalin-fixed, paraffin-embedded tissue and are easily used in routine diagnostic procedures.

PMID: 7913577 [PubMed - indexed for MEDLINE]



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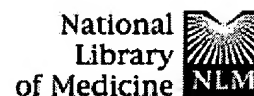
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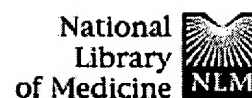
An immunohistologic evaluation of C-erbB-2 gene product in patients with urinary bladder carcinoma.

Sato K, Moriyama M, Mori S, Saito M, Watanuki T, Terada K, Okuhara E, Akiyama T, Toyoshima K, Yamamoto T, et al.

Department of Urology, Akita University School of Medicine, Japan.

BACKGROUND. Amplification or overexpression of the c-erbB-2 gene have been reported to correlate with poor patient prognosis in human breast, gastric, and ovarian cancer. Recently, the c-erbB-2 gene product was found to be expressed frequently in the urinary bladder carcinoma. In the current study, the presence of the c-erbB-2 gene product in urinary bladder carcinomas was compared with patient outcome to evaluate whether c-erbB-2 gene product could identify a subset of patients who are destined to have a poor prognosis. **METHODS.** Immunohistologic study of the c-erbB-2 gene product was done in formaldehyde-fixed paraffin-embedded tissue specimens obtained from 88 transitional cell carcinomas of the human urinary bladder. Eighty-three patients who underwent complete tumor resection by total cystoprostatectomy (30 patients) or by bladder-preserving operations such as transurethral surgery (50 patients) or partial cystectomy (3 patients) entered a follow-up study. The other five patients did not enter the follow-up study because of lost follow-up (2 patients) or distant metastasis at the time of surgery. **RESULTS.** The c-erbB-2 gene product was expressed in 23 of 88 patients (26%), showing an increase in the expression rate corresponding to the advancement of tumor grade ($P < 0.05$) and tumor stage ($P < 0.2$). The 5-year disease-free survival rate was 48.5% for patients with c-erbB-2 negative tumors versus 9.7% for those with c-erbB-2 positive tumors ($P < 0.01$). The 5-year actuarial survival rate was 65.5% for patients with c-erbB-2 negative tumors versus 41.8% for those with c-erbB-2 positive tumors ($P < 0.05$). Multivariate analysis using Cox regression model showed that the c-erbB-2 gene product tissue status was a significant prognostic factor independent of grade and stage of the tumor. **CONCLUSIONS.** The results suggest that the c-erbB-2 gene product could be a tumor marker to identify a malignant subgroup in bladder carcinomas.

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Immunohistochemical detection of c-erbB-2 expression by neoplastic human tissue using monospecific and bispecific monoclonal antibodies.

Garcia de Palazzo I, Klein-Szanto A, Weiner LM.

Fox Chase Cancer Center, Philadelphia, PA 19111.

Selected murine monoclonal antibodies (MAb) have been shown to inhibit relevant tumor growth in vitro and in animal models. Recently, bispecific antibodies (BsMAb) have been developed which target cytolytic effector cells via one antibody binding site and tumor antigen by the other specificity. For example, the BsMAb 2B1 possesses specificity for c-erbB-2 and Fc gamma RIII, the low affinity Fc gamma receptor expressed by polymorphonuclear leukocytes (PMN), macrophages and large granular lymphocytes (LGL). The human homologue of the rat neu oncogene, c-erbB-2, has been demonstrated to be amplified in breast, gastrointestinal, lung and ovarian carcinomas. Tumor expression of c-erbB-2 has been shown to be an important prognostic indicator in breast and ovarian carcinomas. The restricted expression of the c-erbB-2 protooncogene product in normal human tissues and the wide distribution of c-erbB-2 expression in such tumors may justify attempts to use an appropriately constructed BsMAb in clinical trials. In this report we have addressed this issue by immunohistochemically evaluating the expression of c-erbB-2 oncogene product in a variety of malignant tumors utilizing 2B1 and the anti-c-erbB-2 monovalent parent of 2B1, 520C9. Among the studied neoplasms, c-erbB-2 expression was detected in 49% of primary carcinomas stained with 520C9 and in 39% of those stained with 2B1. In the group of metastatic tumors, c-erbB-2 oncoprotein was detected in 52% of cases by 520C9 and in 41% by 2B1.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 7908024 [PubMed - indexed for MEDLINE]

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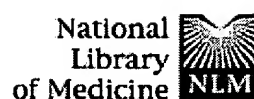


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☐ 1: Cancer Res 1994 Jun 15;54(12):3260-6[Related Articles, Books, LinkOut](#)

c-erbB-2/neu overexpression enhances metastatic potential of human lung cancer cells by induction of metastasis-associated properties.

Yu D, Wang SS, Dulski KM, Tsai CM, Nicolson GL, Hung MC.

Department of Tumor Biology, University of Texas M. D. Anderson Cancer Center, Houston 77030.

Previously, we and others have reported high levels of expression of the c-erbB-2/neu gene in non-small cell lung cancer cell lines and primary tumors. We have also found that expression of c-erbB-2/neu-encoded p185neu was correlated with lymph node metastasis in lung squamous cell carcinomas. To investigate the potential role of the c-erbB-2/neu gene in lung cancer metastasis systematically, we introduced the human c-erbB-2/neu gene into very low p185neu-expressing NCI-H460 human non-small cell lung cancer cells and then examined the experimental metastatic potentials among the parental NCI-H460 cells and stable transfectants with increased expression of p185neu. Compared with the parental NCI-H460 cells, the NCI-H460 transfectants overexpressing p185neu produced significantly more pulmonary and extrapulmonary metastatic tumors in nude mice. The changes in experimental metastatic potential in vivo were accompanied by increased invasiveness in vitro. In addition, important steps in the invasion and metastasis process, such as secretion of basement membrane-degradative enzymes and migration through reconstituted basement membrane (Matrigel), were also increased in the NCI-H460 transfectants overexpressing p185neu. Moreover, scanning electron microscopy revealed that the p185neu-overexpressing NCI-H460 transfectants had significantly more microvilli and membrane protrusions than the parental cells, correlating with the increased invasive properties of these cells. The results demonstrate that overexpression of p185neu can enhance the experimental metastatic potential of NCI-H460 human lung cancer cells by promoting invasion and the other steps in the metastatic cascade.

PMID: 7911396 [PubMed - indexed for MEDLINE]



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HER2 (c-erbB-2) oncoprotein expression in colorectal adenocarcinoma: an immunohistological study using three different antibodies.

Arnaout AH, Dawson PM, Soomro S, Taylor P, Theodorou NA, Feldmann M, Fendly BM, Shepard HM, Shousha S.

Department of Histopathology, Charing Cross Hospital, Charing Cross and Westminster Medical School, London.

Paraffin wax sections of 70 surgically resected colorectal adenocarcinomas were examined for the overexpression of HER2/c-erbB-2 oncoprotein using three different specific antibodies and the avidin-biotin immunoperoxidase technique. The patients included 38 men and 32 women aged between 47 and 80 years. The tumours were derived from various parts of the large intestinal tract, and represented all three stages of Dukes' classification and the three histological grades of differentiation. Many tumour sections also included adjacent normal or transitional mucosa. Eight tubular adenomas found in the colectomy specimens in association with some carcinomas were also examined. No positive membrane staining was seen in any of the 70 carcinomas, four adenomas, two hyperplastic polyps, nor in the adjacent normal or transitional mucosa. It is suggested that the overexpression of c-erbB-2 gene product is unlikely to be as common and as pronounced in colorectal adenocarcinoma as it is in ductal carcinoma of the breast.

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The influence of sucrose, dextran, and hydroxypropyl-beta-cyclodextrin as lyoprotectants for a freeze-dried mouse IgG2a monoclonal antibody (MN12).

Ressing ME, Jiskoot W, Talsma H, van Ingen CW, Beuvery EC, Crommelin DJ.

Laboratory for Inactivated Viral Vaccines, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.

The influence of lyophilization on the stability of a monoclonal antibody (MN12) was investigated. MN12 was freeze-dried in different formulations [without lyoprotectant or in the presence of sucrose, dextran, or hydroxypropyl-beta-cyclodextrin (HP beta CD)] and under varying conditions (with or without secondary drying). Subsequently, the monoclonal antibody was stored for 18 or 32 days at various temperatures (4, 37, or 56 degrees C). For comparison, solutions of MN12 were stored under the same conditions. Regardless of the lyoprotectant used, precipitation and a concomitant reduction of the antigen-binding capacity by about 10% were observed upon reconstitution of lyophilized MN12. HP beta beta CD proved to be the most effective stabilizer to prevent degradation of lyophilized MN12 during storage. Compared with MN12 solutions, HP beta CD-containing lyophilized MN12 cakes were more resistant to heat-induced charge alterations and loss of antigen-binding capacity.

PMID: 1372732 [PubMed - indexed for MEDLINE]

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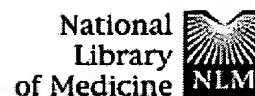
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Stability of freeze dried horseradish peroxidase conjugated monoclonal antibodies used in diagnostic serology.

Nielsen K.

Agriculture and Agri-Food Canada, Animal Diseases Research Institute, Nepean, Ontario, Canada.

Two murine monoclonal antibodies, an IgG1 isotype specific for the heavy chain of bovine IgG1, the second an IgG3 isotype and specific for an epitope of the O-polysaccharide of *Brucella abortus* were conjugated with horseradish peroxidase. The conjugated antibodies were freeze dried in the presence of a number of additives to preserve activity and tested for stability over an 18 month period. Addition of 0.3M trehalose or 0.8% lactalbumin and 3.2% sucrose resulted in the lowest loss of activity if the conjugated antibodies were freeze dried in glass vials. Freeze drying in polypropylene vials resulted in a more rapid rate of deterioration with some additives or an accelerated rate of decline after an initial plateau of lesser loss of activity. The use of polypropylene vials and lactalbumin and sucrose were included in this study because of their low cost compared to glass vials and trehalose. While each antibody behaved differently, addition of trehalose or lactalbumin and sucrose to the conjugated antibodies aided in the preservation of enzyme activity. Both additives provide a suitable method for long term storage of freeze dried or freeze dried and reconstituted monoclonal antibody-enzyme conjugates.

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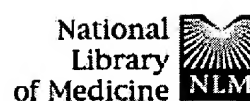
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**A specific molar ratio of stabilizer to protein is required for storage stability of a lyophilized monoclonal antibody.****Cleland JL, Lam X, Kendrick B, Yang J, Yang TH, Overcashier D, Brooks D, Hsu C, Carpenter JF.**

Pharmaceutical R & D, Genentech, Inc., 1 DNA Way, South San Francisco, California 94070, USA. cleland@gene.com

The selection of the appropriate excipient and the amount of excipient required to achieve a 2-year shelf-life is often done by using iso-osmotic concentrations of excipients such as sugars (e.g., 275 mM sucrose or trehalose) and salts. Excipients used for freeze-dried protein formulations are selected for their ability to prevent protein denaturation during the freeze-drying process as well as during storage. Using a model recombinant humanized monoclonal antibody (rhuMAb HER2), we assessed the impact of lyoprotectants, sucrose, and trehalose, alone or in combination with mannitol, on the storage stability at 40 degrees C. Molar ratios of sugar to protein were used, and the stability of the resulting lyophilized formulations was determined by measuring aggregation, deamidation, and oxidation of the reconstituted protein and by infrared (IR) spectroscopy (secondary structure) of the dried protein. A 360:1 molar ratio of lyoprotectant to protein was required for storage stability of the protein, and the sugar concentration was 3-4-fold below the iso-osmotic concentration typically used in formulations. Formulations with combinations of sucrose (20 mM) or trehalose (20 mM) and mannitol (40 mM) had comparable stability to those with sucrose or trehalose alone at 60 mM concentration. A formulation with 60 mM mannitol alone provided slightly less protection during storage than 60 mM sucrose or trehalose. The disaccharide/mannitol formulations also inhibited deamidation during storage to a greater extent than the lyoprotectant formulations alone. The reduction in aggregation and deamidation during storage correlated directly with inhibition of unfolding during lyophilization, as assessed by IR spectroscopy. Thus, it appears that the protein must be retained in its native-like state during freeze-drying to assure storage stability in the dried solid. Long-term studies (23-54 months) performed at 40 degrees C revealed that the appropriate molar ratio of sugar to protein stabilized against aggregation and deamidation for up to 33

months. Therefore, long-term storage at room temperature or above may be achieved by proper selection of the molar ratio and sugar mixture. Overall, a specific sugar/protein molar ratio was sufficient to provide storage stability of rhuMAb HER2.

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